In the Specification

Please substitute the following paragraph for the fifth paragraph starting on page 18 of the specification.

Page 18, paragraph 5 (Currently Amended)

Examples of the "condensed polycyclic aromatic hetero rings" include 9 to 14 membered, preferably, 9 or 10 membered, condensed polycyclic aromatic hetero rings containing one or more (for instance, 1 to 4 atoms) hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Concrete examples of the "condensed polycyclic aromatic hetero rings" include benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiadine, phenoxazine, ~~phthaladine~~ **phthalazine**, naphthylidine, quinazoline, cinnoline, carbazole, β- carboline, acridine, phenazine, phthalimide, thioxanthene.

Please substitute the following paragraph for the fourth paragraph starting on page 21 of the specification.

Page 21, paragraph 4 (Currently Amended)

Concretely, dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, indoline, isoindoline, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiadine, hexahydrophenoxazine, ~~tetrahydrophthaladine~~ **tetrahydrophthalazine**, tetrahydronaphthylidine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro-β-carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxantene, etc., can be mentioned.

Please substitute the following paragraph for the sixth paragraph on page 27 of the specification.

Page 27, paragraph 6 (Currently Amended)

Examples of the "5 to 7 membered saturated cyclic amino" in the above "5 to 7 membered saturated cyclic amino which may have substituents" include morpholino, thiomorpholino, piperazin-1-yl, piperidino, ~~pirrolidin-1-yl~~ **pyrrolidin-1-yl**. The "5 to 7 membered saturated cyclic amino" can be condensed with a benzene ring.

Please substitute the following paragraph for the fourth paragraph on page 33 of the specification.

Page 33, paragraph 4 (Currently Amended)

Examples of "5 to 6 membered hetero ring-carbonyl" in the above "5 to 6 membered hetero ring-carbonyl which may have substituents" include nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, ~~molpholinocarbonyl, pepiridinocarbonyl~~ **morpholinocarbonyl, piperidinocarbonyl**, pyrrolidin-1-ylcarbonyl.

Please substitute the following paragraph for the fifth paragraph on page 33 of the specification.

Page 33, paragraph 5 (Currently Amended)

Examples of the "5 to 6 membered hetero ring-carbamoyl" in the above "5 to 6 membered hetero ring-carbamoyl which may have substituents" include ~~molpholinocarbamoyl, pepiridinocarbamoyl~~ **morpholinocarbamoyl, piperidinocarbamoyl**, 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl.

Please substitute the following paragraph for the third paragraph starting on page 42 of the specification.

Page 42, paragraph 3 (Currently Amended)

Ar^1 is preferably phenyl, biphenylyl (preferably 4-biphenylyl, 2-biphenylyl), phenyl-pyridyl (preferably 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl), phenyl-furyl (preferably 5-phenyl-2-furyl), phenyl-isoxazolyl (preferably 3-phenyl-isoxazol-5-yl), diphenyl-oxazolyl (preferably 2,4-diphenyl-1,3-oxazol-5-yl), pyridyl-phenyl (preferably 4-(4-pyridyl)phenyl, 4-(3-pyridyl)phenyl), phenyl-pyrimidinyl (preferably 2-phenyl-5-pyrimidinyl), benzofuranyl-phenyl (preferably 4-(2-benzofuranyl)phenyl), furyl-phenyl (preferably 4-(2-furyl)phenyl), terphenyl (preferably 4,4'-terphenyl), thienyl-phenyl (preferably 4-(2-thienyl)phenyl), indolyl (preferably 2-indolyl, 3-indolyl), naphthyl-oxadiazolyl (preferably 3-(2-naphthyl)-1,2,4-oxadiazol-5-yl), benzofuranyl-oxadiazole (preferably 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl), benzothienyl (preferably 2-benzothienyl), benzofuranyl (preferably 2-benzofuranyl), fluorenyl (preferably 2-fluorenyl), pyridyl-pyrrolyl (preferably 3-(4-pyridyl)pyrrolyl), thioxanthenyl;
each of which may have 1 to 3 (preferably 1 or 2) substituents selected from the group consisting of halogen atom (preferably fluorine, chlorine, bromine, etc.); nitro; C_{1-3} alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, propyl, trifluoromethyl, etc.); hydroxy-C_{1-6} alkyl (preferably hydroxymethyl, etc.); optionally halogenated C_{3-6} cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C_{1-6} alkythio (preferably methylthio, etc.); hydroxy; C_{7-19} aralkyloxy which may have substituents (preferably, 1 to 3 substituents selected from halogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, etc.) (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy, etc.); C_{6-14}

aryloxy which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenyloxy, 4-methoxyphenyloxy, etc.); amino; mono-C_{1-6} alkylamino (preferably methylamino, etc.); di-C_{1-6} alkylamino (preferably dimethylamino, etc.); 5 to 7 membered saturated cyclic amino which may have substituents (preferably 1 to 3 oxo) and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5 to 7 membered non-aromatic heterocyclic groups which may have substituents (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C_{6-14} aryl-carbonyl which may have substituents (preferably benzoyl, etc.); C_{6-14} aryl-carbamoyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic hetero ring-carbamoyl which may have substituents (e.g. ~~2-pridinylcarbamoyl~~ 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C_{1-6} alkyl-carboxamide (preferably, methylcarboxamide, trifluoromethylcarboxamide, isopropylcarboxamide, etc.); C_{6-14} aryl-carboxamide which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may have substituents (preferably benzylcarboxamide, etc.); aromatic hetero ring-carboxamide which may have substituents (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.))-N-C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may have substituents (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may have substituents (preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxyphenylsulfonylamino, etc.); C_{6-14} aryl-carbonyloxy which may have substituents

(preferably, 1 to 3 optionally halogenated C_{1-6} alkoxy, etc.) (preferably 4-methoxybenzoyloxy, etc.); oxo; carboxy-C_{1-6} alkyl (preferably carboxyethyl, etc.); C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl (preferably methoxycarbonylmethyl, etc.); C_{7-19} aralkyl which may have substituents (preferably 1 to 3 halogen atom) (preferably benzyl, 2,4-dichlorobenzyl, etc.); aromatic hetero ring-C_{1-6} alkoxy (preferably 2-qunolylmethoxy, etc.); and cyano.

Please substitute the following paragraph for the ninth paragraph starting on page 47 of the specification.

Page 47, paragraph 9 (Currently Amended)

As the "bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups", for instance, bivalent groups formed by removing an optional two hydrogen atoms from C_{5-8} cycloalkane or C_{5-8} cycloalkene, can be mentioned. Concrete examples include 1,2-cyclopentylene; 1,3-cyclopentylene; 1,2-cyclohexylene; 1,3-cyclohexylene; 1,4-cyclohexylene; 1,2-cycloheptylene; 1,3-cycloheptylene; 1,4-cycloheptylene; ~~3-cyclohxen-1,4-ylene~~ **3-cyclohexen-1,4-ylene**; 3-cyclohexen-1,2-ylene; 2,5-cyclohexadien-1,4-ylene. Especially, C_{5-8} cycloalkylene is preferable.

Please substitute the following paragraph for the third paragraph on page 50 of the specification.

Page 50, paragraph 3 (Currently Amended)

Examples of the "4 to 8 membered monocyclic non-aromatic hetero rings" include azetidine, pyrrolidine, pyrroline, pyrazolidine, 2- or 3-pyrazoline, imidazoline, piperidine, piperazine, azepine, ~~azokane~~ **azocane**, oxane, oxine, oxepane, oxazolidine, 2-oxazoline, thiazolidine, 2-thioazoline, morpholine, thiomorpholine.

Please substitute the following paragraph for the third paragraph starting on page 60 of the specification.

Page 60, paragraph 3 (Currently Amended)

A prodrug of compound (I') is a compound which is converted to compound (I') by reactions involving enzymes and gastric acid, etc. under physiological conditions in the living body; in other words, a compound that is changed into compound (I') by enzymatically-caused oxidation, reduction and hydrolysis, and a compound that is changed into compound (I') by hydrolysis caused by gastric acid. Examples of the prodrugs of compound (I') include compounds in which amino groups of compound (I') have been acylated, alkylated, or phosphorylated [e.g. compounds in which amino groups of compound (I') have been eicosanoylated, ~~aranylated~~ **alanylated**, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated, etc.]; compounds in which hydroxyl groups of compound (I') have been acylated, alkylated, phosphorylated, borated (e.g. compounds in which hydroxyl groups of compound (I') have been acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, ~~fumarilated, alanilated~~ **fumarylated, alanylated**, dimethylaminomethylcarbonylated, etc.); compounds in which carboxyl groups of compound (I') have been esterified or amidated [e.g. compounds in which carboxyl groups of compound (I') have been ethylesterified, phenylesterified, carboxylmethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified, or methylamidated, etc.]. These compounds can be produced from compound (I') using per se known methods.

Please substitute the following paragraph for the second paragraph on page 73 of the specification.

Page 73, paragraph 2 (Currently Amended)

Examples of the above "ketone ~~solventd~~ **solvents**" include acetone, methylethylketone.

Please substitute the following paragraph for the third paragraph starting on page 88 of the specification.

Page 88, paragraph 3 (Currently Amended)

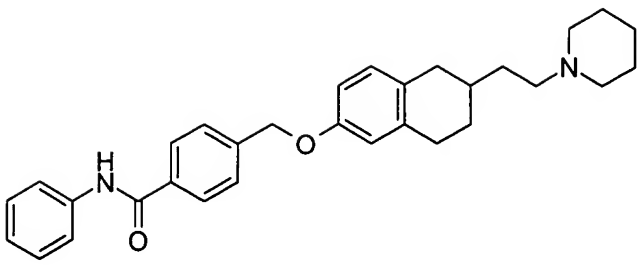
Diethyl azodicarboxylate (40% toluene solution, 0.95 g) was added dropwise to THF solution (6 ml) of 2-(R)-[2-(N,N-dimethylamino)ethyl]-6-hydroxytetralin (300 mg), 4-(hydroxymethyl)phenyl 4-methoxybenzoate (530 mg), and triphenylphosphine (430 mg) under ice-cooling. After stirring for 2 hours at room temperature, the reaction mixture was concentrated. The residue was purified using ~~almina~~ **alumina** column chromatography (development solvent; hexane ~ hexane : ethyl acetate = 10:1), and the titled compound (320 mg) was obtained after recrystallization (ethyl acetate-hexane).

Melting point: 111 - 114°C

$[\alpha]_D^{20}$ = +44.4° (c = 0.502, methanol)

Reference Example 2

N-Phenyl-4-[[2-(2-piperidinoethyl)-6-tetralinyl]oxymethyl]benzamide



Please substitute the following paragraph for the second paragraph on page 104 of the specification.

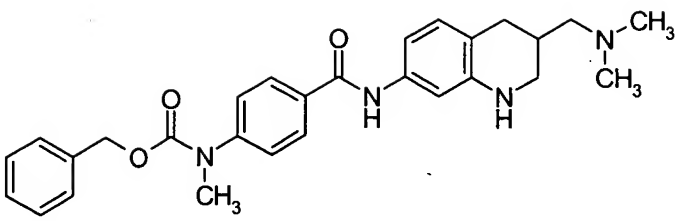
Page 104, paragraph 2 (Currently Amended)

One drop of DMF was added to THF solution of 4-biphenylylcarboxylic acid (145 mg), and oxalyl chloride (0.1 ml) was added dropwise to the solution under ice-cooling, which was stirred at room temperature for 30 minutes. After the reaction mixture was concentrated, the residue was dissolved in THF (1 ml), which was added dropwise to pyridine solution (1.5 ml) of 7-amino-3-[(N,N-dimethylamino)methyl]-1,2,3,4- ~~tetrahydoquinoline~~ **tetrahydroquinoline** (150 mg) under ice-cooling, and the reaction mixture was stirred for 30 minutes. After the temperature of the reaction mixture was raised to room temperature, 10% aqueous potassium carbonate was added to the reaction mixture, and extraction was conducted using a mixed solution of THF and ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried, and then concentrated. The residue was recrystallized using THF-IPE to give the titled compound (180 mg).

Melting point: 206 - 211°C

Reference Example 27

4-[N-[(Benzyloxy)carbonyl]-N-methylamino]-N-[3-[(N,N-dimethylamino)methyl]-1,2,3,4-tetrahydo-7-quinolinyl]benzamide



Please substitute the following paragraph for the third paragraph starting on page 133 of the specification.

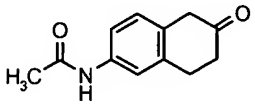
Page 133, paragraph 3 (Currently Amended)

~~Trimethylsillylnitrile~~ **Trimethylsilylnitrile** (1.02 ml, 7.68 mmol) and zinc iodide (22 mg, 0.0698 mmol) were added to dichloroethane solution (9 ml) of 6-acetylamino-2-(1-pyrrolidinylmethyl)-1-tetralone (1.00 g, 3.49 mmol) obtained in Reference Example 69-2), which was stirred at room temperature for 2 days. The solvent was distilled out under reduced pressure. Ethyl acetate was added to the obtained oily substance, which was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled out under reduced pressure. The resulting residue was purified by alumina column chromatography (development solvent ; ethyl acetate), to give ~~trimethylsillylcyanohydrin~~ **trimethylsilylcyanohydrin** form (1.21 g) as an oily substance. 2.5N Hydrochloric acid was added to the oily substance (978 mg, 2.73 mmol), which was stirred at 100℃ for 1.5 hours. The aqueous solution obtained was washed with ethyl acetate. Potassium carbonate was added to the water layer to make it alkaline, and extraction was conducted using ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled out under reduced pressure. The resulting oily substance was purified by alumina column chromatography (development solvent ; hexane : ethyl acetate = 5:1) , to give the titled compound (358 mg).

^{1}H NMR ($CDCl_3$) δ : 1.80 (4H, m), 2.56 (6H, m), 3.73 (2H, m), 3.50 (2H, s), 3.77 (2H, br), 6.46 (1H, s), 6.55 (1H, d, J = 8.1 Hz), 7.26 (1H, d, J = 8.1 Hz).

Reference Example 71

6-Acetamido-2-tetralone



Please substitute the following paragraph for the second paragraph starting on page 159 of the specification.

Page 159, paragraph 2 (Currently Amended)

1) 2-Ethoxycarbonyl-6-nitro-1,4-benzoxazine (7.20 g, 0.029 mol) obtained by a known ~~method by documents~~ **literature method** (~~Journal of heterocyclic chemistry~~ **Journal of Heterocyclic Chemistry**, 19(5), p.1189 (1982)) was ~~dissolves~~ **dissolved** in methanol (50 ml). Sodium borohydride (1.08 g, 0.029 mol) was added to the solution, which was stirred for 2 hours. The reaction mixture was concentrated. Ethyl acetate and aqueous potassium hydrogencarbonate solution were added to the residue, and extraction was conducted. The organic layer was washed with water, and concentrated. A mixed solution of ethyl acetate and n-hexane (1:5) was added to the residue for crystallization. The crystallized product was collected by filtration, to give 2-hydroxymethyl-6-nitro-1,4-benzoxazine (3.10 g) as a red powder. ^{1}H-NMR ($CDCl_3$) δ : 1.96 (1H, m), 3.34-3.49 (2H, m), 3.80-3.90 (2H, m), 4.09 (1H, brs), 4.30-4.40 (1H, m), 6.86 (1H, d, J=8.6 Hz), 7.50 (1H, d, J=2.8 Hz), 7.59 (1H, dd, J=2.8, 8.6 Hz).

Please substitute the following paragraph for the third paragraph starting on page 206 of the specification.

Page 206, paragraph 3 (Currently Amended)

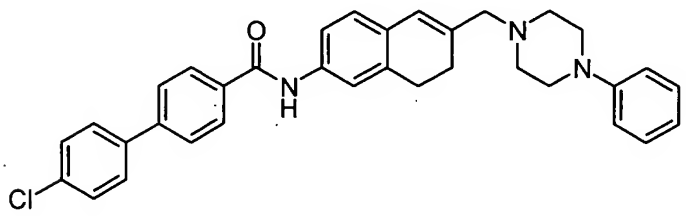
The titled compound was obtained by carrying out the same operation as in Example 51, using 4'-chloro-N-[6-(chloromethyl)-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide obtained in Reference Example 56.

^{1}H NMR ($CDCl_3$) δ : 2.20-2.30 (2H, m), 2.25 (3H, s), 2.85-2.90 (2H, m), 3.00 (2H, s), 6.30 (1H, s), 6.74-7.95 (146H, m).

Melting point: 177 - 179°C (crystallization solvent: tetrahydrofuran - n-hexane)

Example 68

4'-Chloro-N-[6-[(4-phenyl-1- ~~**piperadinyl**~~ **piperazinyl**)methyl]-7,8-dihydro-2-naphthalenyl][1,1'-biphenyl]-4-carboxamide



Please substitute the following paragraph for the second paragraph starting on page 223 of the specification.

Page 223, paragraph 2 (Currently Amended)

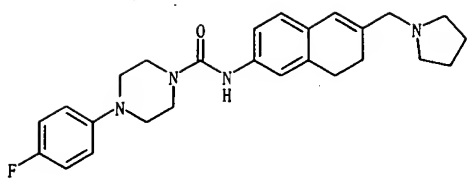
6-(1-Pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenamine obtained in Reference Example 54 (50 mg, 0.22 mmol) and pyridine (35 mg, 0.44 mmol) were dissolved in tetrahydrofuran (3 ml). Phenyl chlorocarbonate (38 mg, 0.24 mol) was added to the solution under ice-cooling, which was stirred for 10 minutes. The reaction mixture was concentrated, and ~~dimehtylsulfoxide~~ **dimethylsulfoxide** (5 ml) was added to the residue. 4-(4-Fluorophenyl)piperidine hydrochloride (57 mg, 0.26 mmol) and 4N aqueous sodium hydroxide solution (0.066 ml, 0.26 mmol) were added to the reaction mixture at room temperature while stirring, which was stirred for 30 minutes. Ethyl acetate and water were added to the mixture, and extraction was conducted. The organic layer was washed with water, and concentrated. Diisopropyl ether was added to the residue. The crystallized product was collected by filtration, washed with diisopropyl ether, to give 4-(4-fluorophenyl)-N-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide (48 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ : 1.60-1.70 (2H, m), 1.79 (4H, m), 1.80-1.90 (2H, m), 2.33 (2H, t, J=7.8 Hz), 2.51 (4H, m), 2.60-2.70 (1H, m), 2.80 (2H, t, J=7.8 Hz), 2.90-3.10 (2H, m), 3.16 (2H, s), 4.18-4.23 (2H, m), 6.32 (1H, s), 6.32 (1H, s), 6.92-7.09 (4H, m), 7.15-7.20 (3H, m).

Melting point: 182 - 185°C (crystallization solvent : diisopropyl ether)

Example 100

4-(4-Fluorophenyl)-N-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]-1-piperazinecarboxamide



Please substitute the following paragraph for the third paragraph starting on page 224 of the specification.

Page 224, paragraph 3 (Currently Amended)

1) 6-Cyano-1-tetralone (1.30 g, 7.59 mmol) synthesized by a known ~~method by documents~~ literature method (~~synthetic communications~~ Synthetic Communications, 23(21), 2965 (1993)) was dissolved in a mixed solution of concentrated hydrochloric acid (10 ml) and acetic acid (20 ml), which was stirred at 120℃ for 16 hours. The reaction mixture was concentrated. Ethyl acetate and water were added to the residue, and extraction was conducted. The organic layer was washed with water, and concentrated. The residue was washed with ethyl acetate - n-hexane (1:1), to give 5-oxo-5,6,7,8-tetrahydro-2-naphthalenecarboxylic acid (1.10 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ : 2.15-2.23 (2H, m), 2.70-2.75 (2H, m), 3.04-3.07 (2H, m), 8.01-8.03 (1H, m), 8.03 (1H, s), 8.13 (1H, d, J=8.7 Hz).

Please substitute the following paragraph for the second paragraph starting on page 318 of the specification.

Page 318, paragraph 2 (Currently Amended)

The titled compound was obtained by carrying out the same operation as in Reference Example 99, using 5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenamine obtained in Reference Example 115.

^{1}H NMR ($CDCl_3$) δ: 1.60-1.78 (4H, m), 2.05 (3H, s), 2.28 (3H, s), 2.29 (2H, t, J=8.1 Hz), 2.33 (3H, s), 2.46 (8H, bs), 2.65-2.72 (3H, m), 2.93-3.03 (2H, m), 3.13 (2H, s), 4.18-4.23 (2H, m), 6.40 (1H, s), 7.09-7.24 (7H, m).

Melting point: 176-178 °C (crystallization solvent:ethyl ~~acetaten-hexane~~ **acetate n-hexane**)

Example 260

4-(4-Methoxyphenyl)-N-[5-methyl-6-[(4-methyl-1-piperazinyl)methyl]-7,8-dihydro-2-naphthalenyl]-1-piperidinecarboxamide